

1

**Compositions and Uses Thereof**

2

**Field of the Invention**

4

5 The present invention relates to methods of  
6 controlling serum glucose levels in mammals. In  
7 particular it relates to methods for the prevention  
8 of severe fluctuations in glucose levels and the use  
9 of these methods in the treatment of diseases  
10 characterised by hypoglycaemia, such as glycogen  
11 storage disease (GSD), clinical conditions where a  
12 slow release of energy in the form of glucose may be  
13 required (e.g. diabetes) and for sports and fitness  
14 type products where a slow release of energy is  
15 desirable.

16

**Background to the Invention**

18

19 The release of energy from foods and food products  
20 is a complex process. It depends on the composition,  
21 structure, extent of modification and volume of the  
22 food. Apart from this, it is also variable between

1 individuals and reflects many different factors  
2 which probably include a combination of age, level  
3 of fitness, rate of gastric emptying and  
4 peristalsis, sex, size, state of health etc. Energy  
5 may be derived from different food sources, for  
6 example, carbohydrates, lipids and proteins, alcohol  
7 etc. In many animals, including man, energy is  
8 stored as fat (adipose tissue) and provides a  
9 reserve when food is limiting. There is a more  
10 readily available form of energy, however, where a  
11 glucose polymer (glycogen) is stored in muscles and  
12 the liver and can be rapidly mobilised when  
13 required. The formation and storage of glycogen is a  
14 synchronised enzymatic process which is controlled  
15 in part by insulin which promotes the formation of  
16 glycogen from the glucose precursors (Figure 1).  
17 Glucose deposition and glycogen catabolism is co-  
18 ordinated in man to maintain blood glucose at  
19 ~4.5mmol l<sup>-1</sup>.

20

#### 21 *Glycogen storage disease*

22

23 In the normal human, the anabolism and catabolism of  
24 glycogen is normally co-ordinated and regulated. The  
25 deposition of glycogen is promoted by insulin whilst  
26 the hydrolysis of glycogen and conversion to glucose  
27 is promoted by adrenaline (especially muscle) and  
28 glucagons (especially liver).

29

30 In glycogen storage disease (GSD) there is an  
31 inherited defect with respect to the deposition or  
32 hydrolysis of glycogen

1       (<http://www.agasd.org.uk/home/information.asp>;  
2       [http://agsdus.org/body\\_whatis\\_1.html](http://agsdus.org/body_whatis_1.html)) and  
3       consequently the concentration of blood glucose.  
4       Figure 1 outlines the principles of glycogen  
5       metabolism.

6

7       The most common types of glycogen storage disease  
8       are:

9

10       In Type I (Von Gierke Disease) individuals suffer  
11       from a lack of glucose-6-phosphatase activity ('h'  
12       in Figure 1) and hence cannot generate glucose from  
13       glycogen. Consequently they need to be tube fed to  
14       maintain blood glucose.

15       In Type II (Pompe's Disease) individuals suffer  
16       from a lack of  $\alpha$ -glucosidase activity ('i' in Figure  
17       1). Infants often die of this form very young.

18       In Type III (Cori's Disease) individuals suffer  
19       from a lack of debranching enzyme activity ('i' in  
20       Figure 1). Treatment usually consists of a high  
21       protein diet.

22       In Type IV (Anderson's Disease) individuals  
23       suffer from a lack of branching enzyme activity ('e'  
24       in Figure 1). Liver transplantation is the only  
25       viable therapy.

26       In Type V (McArdle's Disease) individuals suffer  
27       from a lack of muscle phosphorylase activity ('f' in  
28       Figure 1). Extensive exercise should be avoided.

29       In Type VI (Her's Disease) individuals suffer  
30       from a lack of liver phosphorylase activity ('f' in  
31       Figure 1). There is a male X- chromosome link.

1        In Type VII (Tarui's Disease) individuals suffer  
2        from a lack of muscle phosphofructokinase activity.  
3        Extensive exercise should be avoided.

4        In Type IX individuals suffer from a lack of  
5        liver phosphorylase activity ('f' in Figure 1).  
6        There is a male X- chromosome link and it is  
7        comparable to type VI.

8

9        Low blood glucose can be treated by the slow  
10      administration of glucose (oral or intra-venous), or  
11      from starch hydrolysates (e.g. maltose, dextrins  
12      etc.) or from native starch where glucose is  
13      liberated as a consequence of digestion. In practice  
14      'corn-starch', which is normal maize starch, is used  
15      to treat glycogen storage disease (especially during  
16      sleep) due to availability and to lack of a superior  
17      alternative in terms of digestive response. The  
18      starch must be slowly digested and not converted to  
19      glucose rapidly or excreted with little hydrolysis.  
20      In other clinical conditions (such as diabetes  
21      mellitus) there is also the need to supply glucose  
22      slowly and from a non-sugar based matrix (e.g.  
23      cakes, biscuits, sweets etc.). This can, therefore,  
24      also be achieved by starch (hydrolysis in the gut)  
25      and is important for night time regimes where  
26      glucose is essential in the blood but within a  
27      controlled form.

28

29      The advantages and disadvantages of feeding glucose,  
30      maltodextrins or maize starch for clinical nutrition  
31      with a perceived optimal substrate are defined in  
32      Table 1.

1

2      Table 1. Release profile of glucose based substrates  
 3      in the gut of man with perceived optimised product  
 4      in this respect

5

Entry to body	Glucose	Maltodextrin	Normal maize ('corn') starch	
Intravenous	Used extensively in medicine. Would need to be pumped constantly for GSD and diabetes clinical maintenance.	Too high molecular weight	Inappropriate in view of size, composition and structure	Appropriate in view of size, composition and structure
Oral - small intestine	Rapidly absorbed (1.5 hours)	Rapidly absorbed (1.5 hours)	Glucose released within 4 hours	Glucose released over 7.5 hours (to provide overnight release)
Oral - large intestine	Not applicable	Not applicable	Possibly mostly digested with small amount of fermentable substrate	Minimal fermentable substrate to avoid loss of energy and fermentation

6

7      *Slow release of energy*

8

9      Apart from the clinical conditions described above,  
 10     athletes require sustained release of energy. There

1 are many products on the market which release energy  
2 based on sugars or maltodextrins. These include  
3 products presented in Table 2. However, sugars and  
4 dextrins are absorbed very rapidly and these  
5 products must be consumed regularly to maintain the  
6 required body loading of the energy.

7

8 Table 2. Energy based products currently found on  
9 the market.

10

Product	Carbohydrate, % of product	Carbohydrates used as energy source
Accelerade	7.75	Fructose, maltodextrin and sucrose
Allsport	9.00	High fructose syrup
Cytomax	6.00	High fructose syrup and maltodextrin
Enervit G	7.60	Fructose, glucose, maltodextrin and sucrose
Extran	5.00	Fructose and maltodextrin
thirstquencher		
G Push	7.50	Fructose, galactose and maltodextrin
Gatorade	6.00	Fructose, glucose and sucrose
GU20	5.70	Fructose and maltodextrin
Powerade	8.00	High fructose syrup and glucose polymers [sic]
Revenge Sport	7.00	Fructose, glucose and maltodextrin

11 (adapted from [www.accelerade.com/accelerade-comparison-results.asp](http://www.accelerade.com/accelerade-comparison-results.asp))  
12

1

2

3 *Slow energy release nutritional formulations*

4

5 As mentioned above, slow release products for sports  
6 nutrition tend to be pouches relying on glucose or  
7 maltodextrin to supply the energy. These actually  
8 are absorbed quickly as they are either readily  
9 absorbed (e.g. glucose) or converted to glucose  
10 relatively rapidly (e.g. maltodextrins, probably  
11 within 60 minutes maximum).

12

13 On the other hand, glycogen storage disease (certain  
14 treatable forms, see above) management requires that  
15 patients receive a slow release of glucose,  
16 especially, for example, overnight. Native starch is  
17 provided for this purpose where: the initial  
18 liberation phase of glucose is not too rapid (see  
19 figures below); glucose is released at a constant rate  
20 as possible which must not be too slow or too  
21 fast and; the production of lactate (anaerobic  
22 respiration) is minimised. Certain starches are to  
23 be avoided as they exhibit only limited hydrolysis  
24 in the native form (e.g. potato).

25

26 Hence, the extent and rate of starch digestion are  
27 important parameters with respect to glucose release  
28 from the ingested  $\alpha$ -glucan. Regulation in terms of  
29 these parameters reflect the state of the starch and  
30 the rate at which the energy source travels through  
31 the gut. A balance in terms of energy release is

1 required which can be controlled by the energy  
2 source and the transit time.

3

4 Osmolality is also an important feature with respect  
5 to carbohydrate usage. Sugar solutions exert a high  
6 osmotic pressure compared to polysaccharides due to  
7 the number of moles in solution.

8

9 The viscosity of the consumed material will also  
10 affect the capacity for it to be hydrolysed and to  
11 permit associated compounds to come into contact  
12 with the mucosal surface. This is a very important  
13 issue with respect to product development regarding  
14 potential energy sources.

15

16 Glycaemic Index (GI) is also an important  
17 determinant of energy availability from foods and  
18 more especially  $\alpha$ -glucans. In this context, white  
19 bread has a GI of 1 which is the same as pure  
20 glucose and represents one hundred percent  
21 availability of the  $\alpha$ -glucan fraction (or 1 on a  
22 scale from 0 to 1).

23

24 *Gastric emptying*

25

26 As mentioned above, the rate and extent of gastric  
27 emptying will in part regulate the transit time of  
28 food materials through the gut. It is established  
29 that high volumes - low energy promote gastric  
30 emptying whereas low volumes - high energy restrict  
31 gastric emptying. Lipids and proteins are valuable

1 aids with respect to restricting emptying of the  
2 stomach.

3

4 Glycogen storage disease and diabetes are  
5 classically managed by feeding 'cornstarch' which is  
6 normal maize starch (Kaufman, 2002). Sometimes,  
7 proportions of carbohydrates are utilised which  
8 provide rapid (e.g. sugar), medium (e.g. gelatinised  
9 starch) and slow ('cornstarch') digestion and hence  
10 glucose appearance in the blood (Wilbert, 1998).

11 Sugar combinations with or without maltodextrins or  
12 'glucose polymers' are often employed in 'energy  
13 drinks' (including rehydration drinks) and often  
14 with other components like salts, protein, fatty  
15 acids, glycerol, minerals, flavouring etc. (Gawen,  
16 1981; Tauder et al, 1986; Burling et al, 1989;  
17 Gordeladze, 1997; Paul and Ashmead, 1993 and 1994;  
18 Vinci et al, 1993; Fischer et al, 1994; Simone,  
19 1995; Gordeladze, 1997; King, 1998; Kurppa, 1998;  
20 Cooper et al, 2001; Portman, 2002). The  
21 maltodextrins/ glucose polymers are used to slow  
22 energy availability (compared to sugars) and exert  
23 less osmotic pressure.

24

25 Brynolf et al (1999) describe the production of an  
26 acid modified starch with a molecular weight of  
27 15,000 to 10,000,000 produced by classical acid  
28 hydrolysis of starch to be used as an energy source  
29 prior to physical activity. Lapré et al (1996) have  
30 discussed the option of coating food with non-starch  
31 polysaccharides (cation gelling) to reduce the  
32 glycaemic response of carbohydrate containing foods.

1  
2     However, although currently available starch  
3     preparations used in the treatment of conditions  
4     such as GSD have prolonged glucose release profiles  
5     compared to glucose and maltodextrin based products,  
6     the time period over which the products enable serum  
7     glucose levels to be maintained within an acceptable  
8     range is relatively short. Thus, at present, using  
9     conventional oral preparations, patients susceptible  
10    to hypoglycaemic episodes generally must ingest such  
11    glucose sources at intervals of no longer than 4  
12    hours. Although this may be acceptable during  
13    daytime, the need for repeated feeding is very  
14    inconvenient at nighttime. The patient thus must  
15    either awake or be wakened overnight to feed or,  
16    alternatively, sleep with a nasogastric tube in  
17    place to provide a constant source of glucose.

18  
19    Accordingly, there is a great need for alternative  
20    means of maintaining serum glucose levels within  
21    safe ranges over a longer period of time than that  
22    afforded by the conventional treatments.

23

24    Summary of the Invention

25

26    The present inventors, after considerable work, have  
27    surprisingly discovered that semi-crystalline waxy  
28    starches afford significantly prolonged glucose  
29    release in the human GI tract compared to normal or  
30    high amylose semi-crystalline starches as  
31    conventionally used in preparations for slow energy

1 release.

2

3 Accordingly, in a first aspect, the present  
4 invention provides a method of controlling serum  
5 glucose levels in an individual said method  
6 including the step of administering to said  
7 individual a therapeutic food composition comprising  
8 a waxy starch.

9

10 In a second aspect, the invention provides a method  
11 of treating or preventing hypoglycaemia in an  
12 individual said method including the step of  
13 administering to said individual a therapeutic food  
14 composition comprising a waxy starch.

15

16 According to a third aspect, the invention provides  
17 a method of treating an individual susceptible to  
18 hypoglycaemic episodes, said method including the  
19 step of administering to said individual a  
20 therapeutic food composition comprising a waxy  
21 starch.

22

23 In one preferred embodiment, said treatment is  
24 treatment to prevent or decrease night-time  
25 hypoglycaemic episode(s).

26

27 As described herein, the inventors have found that  
28 waxy starches provide prolonged glucose release when  
29 ingested.

30

31 Moreover, as well as discovering that such semi-  
32 crystalline starches provide advantageous slow

1       glucose release, the inventors have unexpectedly  
2       found that the time period over which glucose may be  
3       released from starches and thus the time period over  
4       which serum glucose levels may be maintained in  
5       patients without the need for further doses of food  
6       compositions can be markedly increased by  
7       hydrothermal treatment of starches for use in the  
8       invention. Indeed, as demonstrated in the Examples  
9       below, the time period over which serum glucose  
10      levels may be maintained in patients without the  
11      need for further doses of food compositions may be  
12      prolonged by use of such hydrothermally treated  
13      starches (for example heat moisture treated  
14      starches) to more than six hours, indeed typically  
15      more than 7 hours. Thus, the use of such starches  
16      (or indeed other hydrothermally treated starches) in  
17      the methods of the invention enables a patient  
18      susceptible to night-time hypoglycaemic episodes to  
19      sleep for a substantially normal duration i.e. more  
20      than 6 hours, preferably more than 7 hours, without  
21      the need for nasogastric feeding or further food  
22      doses throughout the night.

23

24      Accordingly, in preferred embodiments of the  
25      invention, the starch is hydrothermally treated  
26      (HTT) waxy starch. Preferably said hydrothermally  
27      treated waxy starch is heat-moisture treated (HMT)  
28      waxy starch.

29

30      However, as well as finding that hydrothermal  
31      treatment has very advantageous effects on waxy  
32      starches, the inventors have also shown that

1       hydrothermal treatment also improves and prolongs  
2       the glucose release profile of non-waxy starches.

3

4       Accordingly, in a fourth independent aspect of the  
5       present invention, there is provided a method of  
6       controlling serum glucose levels in an individual  
7       said method including the step of administering to  
8       said individual a therapeutic food composition  
9       comprising a hydrothermally treated starch.

10

11      In a fifth aspect, the invention provides a method  
12     of treating or preventing hypoglycaemia in an  
13     individual said method including the step of  
14     administering to said individual a therapeutic food  
15     composition comprising a hydrothermally treated  
16     starch.

17

18      According to a sixth aspect, the invention provides  
19     a method of treating an individual susceptible to  
20     hypoglycaemic episodes to prevent or decrease  
21     hypoglycaemic episode(s), said method including the  
22     step of administering to said individual a  
23     therapeutic food composition comprising  
24     hydrothermally treated starch.

25

26      In one preferred embodiment, said treatment is  
27     treatment to prevent or decrease night-time  
28     hypoglycaemic episode(s).

29

30      In the fourth, fifth and sixth aspects of the  
31     invention, any suitable hydrothermally treated  
32     starch may be used. Said hydrothermally treated

1       starch may be starch which has been heat moisture  
2       treated or starch which has been subjected to  
3       annealing treatment. In preferred embodiments the  
4       hydrothermally treated starch is heat moisture  
5       treated starch.

6

7       In preferred embodiments of the invention, starch of  
8       and for use in the invention is a "waxy starch".

9

10      Waxy starches for use in any aspect of the present  
11      invention may be any starch having an amylopectin  
12      content of at least 70%, preferably at least 80%,  
13      more preferably at least 85%, even more preferably  
14      at least 90%, yet more preferably at least 95%, most  
15      preferably at least 98% amylopectin. Such waxy  
16      starches may be cereal or non-cereal waxy starches.  
17      Preferably, said waxy starch is a waxy cereal  
18      starch, for example waxy maize starch.

19

20      Preferably, the starch of and for use in the  
21      invention should have a granular size in the range  
22      10 to 35 $\mu\text{m}$ , more preferably in the range 15 to 30 $\mu\text{m}$ .

23

24      Preferably the starch used in the invention enables  
25      a blood glucose concentration of greater than 3.0  
26      mmol l<sup>-1</sup> at 300 min post administration.

27

28      In preferred embodiments, the therapeutic food  
29      composition is such that it, in use, its  
30      administration results in a maximum blood glucose  
31      concentration of no greater than 9 mmol l<sup>-1</sup>. In a  
32      further embodiment, in use, administration of the

1       therapeutic food composition results in a maximum  
2       blood glucose concentration of no greater than 8  
3       mmol l<sup>-1</sup>.

4

5       In particularly preferred embodiments, the starch,  
6       in use, enables a blood glucose concentration of  
7       greater than 3.0 mmol l<sup>-1</sup> at 300 min post  
8       administration, but does not cause a peak in blood  
9       glucose concentration of any greater than 9.0 mmol  
10      l<sup>-1</sup>, for example not greater than 8.0 mmol l<sup>-1</sup>

11

12      References to blood glucose concentration relate to  
13      a typical adult human of normal weight, for example  
14      72 kg.

15

16      Preferably therapeutic food compositions of and for  
17      use in the method of the present invention comprise  
18      per unit dose greater than 50g, preferably greater  
19      than 60g , for example more than 70g, even more  
20      preferably greater than 80g, most preferably at  
21      least 90g of the starch.

22

23      In a seventh aspect of the invention, there is  
24      provided the use of a starch in the preparation of a  
25      therapeutic foodstuff for the treatment of  
26      hypoglycaemia, wherein said starch is a waxy and/or  
27      hydrothermally treated starch.

28

29      Also provided by the invention is the use of starch  
30      in the preparation of a therapeutic foodstuff for  
31      the treatment or prevention of hypoglycaemic  
32      episode(s), for example night-time hypoglycaemic

1       episode(s), wherein said starch is a waxy and/or  
2       hydrothermally treated starch.

3

4       Further provided by the invention is a therapeutic  
5       foodstuff comprising a starch, wherein said starch  
6       is a waxy and/or hydrothermally treated starch.

7

8       Therapeutic foodstuffs and food compositions of and  
9       for use in the invention may be provided in kit  
10      form. Accordingly, in a eighth aspect, the  
11      invention provides a therapeutic food kit, said food  
12      kit comprising:

13       a) a therapeutic food composition comprising starch,  
14       wherein said starch is a waxy and/or hydrothermally  
15       treated starch; and  
16       b) instructions for ingesting said therapeutic food  
17       composition.

18

19       The methods and therapeutic foodstuffs of and for  
20       use in the invention may be used to treat  
21       individuals with any disease associated with the  
22       presence or susceptibility to hypoglycaemia. Such  
23       diseases include, but are not limited to diabetes  
24       (Type I or Type II), glycogen storage disease, liver  
25       disease, for example, liver cirrhosis.

26

27       Moreover the methods and therapeutic foodstuffs of  
28       and for use in the invention are not limited to use  
29       with individuals having such disease. The  
30       demonstration by the present inventors that  
31       starches, which are waxy and/or hydrothermally  
32       treated, afford significantly prolonged glucose

1 release in the GI tract compared to normal starches  
2 enables the use of such waxy and/or hydrothermally  
3 treated starches in therapeutic foodstuffs for  
4 sports nutrition, for example, to provide a  
5 sustained release food source during exercise, for  
6 example, prolonged exercise.

7

8 Accordingly, the invention further extends to the  
9 use of a starch in the preparation of sports  
10 nutrition foodstuff, wherein said starch is a waxy  
11 and/or hydrothermally treated starch.

12

13 Further provided by the invention is a sports  
14 nutrition foodstuff comprising a starch, wherein  
15 said starch is a waxy and/or hydrothermally treated  
16 starch.

17

18 Preferred features of each aspect of the invention  
19 are as for each of the other aspects mutatis  
20 mutandis.

21

#### 22 **Detailed description**

23

24 As described above, the present inventors have  
25 discovered that existing treatments for conditions  
26 characterised by hypoglycaemic episodes may be  
27 improved and/or supplemented by the use of waxy  
28 starches as sources of  $\alpha$ -glucan, thus enabling  
29 significant improvement to control over the rate of  
30 glucose formation and appearance in the blood  
31 mammals. Such starches significantly outperform the  
32 conventionally used 'corn starch' (native maize

1 starch) in terms of duration of glucose release due  
2 to amylase hydrolysis in the small intestine.

3

4 Moreover, the inventors have shown that the glucose  
5 release profile may be further dramatically  
6 prolonged by modifications to the optimised starch  
7 e.g. by hydrothermal treatment for example, by heat  
8 moisture treatment. Indeed, hydrothermal treatment  
9 also provides considerable improvement in  
10 conventional non-waxy starches. Thus, the invention  
11 also extends to the methods of the first, second and  
12 third aspect of the invention, wherein the waxy  
13 starch is substituted by any hydrothermally treated  
14 starch , preferably heat moisture treated starch  
15 (whether waxy or non-waxy).

16

17 *Starches*

18

19 Starches are produced by plants as roughly spherical  
20 granules ranging in diameter from <5 to >50 $\mu\text{m}$ .  
21 Depending on source they contain ~11-17% moisture,  
22 ~82-88%  $\alpha$ -glucan, ~1.5% lipid and ~0.6% protein.  
23 The  $\alpha$ -glucan comprises two types of molecules:  
24 amylose and amylopectin. The former is an  
25 essentially linear molecule comprising about 99%  $\alpha$ -  
26 (1-4) and about 1%  $\alpha$ -(1-6) bonds with a molecular  
27 weight of ~500,000. Amylopectin is much bigger than  
28 amylose with a molecular weight of a few million and  
29 is heavily branched with ~95%  $\alpha$ -(1-4) and ~5%  $\alpha$ -(1-  
30 6) bonds. The exterior chains of amylopectin  
31 associate together as double helices which

1       themselves register together to form crystalline  
2       laminates. These crystalline laminates are  
3       interspersed with amorphous material comprising non-  
4       crystalline (branched regions) of amylopectin plus  
5       amylose. The amylose may form inclusion complexes in  
6       cereal starches with lipids causing the presence of  
7       two forms of the molecule: lipid complexed and lipid  
8       free.

9

10      In normal starches, amylopectin is the 'seat' of  
11      crystallinity. Waxy starches have a greater  
12      proportion of crystallinity due to the higher  
13      amylopectin content. High amylose starches contain  
14      both amylopectin and amylose generated crystalline  
15      material.

16

17      Starches containing <~20% amylose (80% amylopectin)  
18      are commonly referred to as 'waxy', ~20-40% are  
19      commonly referred to as 'normal' and ~>40% are  
20      commonly referred to as high amylose or amylo-  
21      starches. Normal maize and wheat starches are, for  
22      example, ~30% amylose.

23

24      The semi-crystalline native starch granules are  
25      insoluble and largely indigestible by man's  
26      digestive enzymes. The control of native starch  
27      digestion in man is not well understood although it  
28      does not provide a major nutritional focus as most  
29      starches are processed prior to cooking. Processing  
30      of starch incorporates cooking in water which  
31      disrupts the crystalline regions and 'gelatinises'  
32      the starch. Gelatinised starches are very digestible

1 because of their amorphous nature by amylases and  
2 related enzymes in the small intestine of man.  
3 Native and resistant starches (see below), although  
4 in part digested in the small intestine, are  
5 fermented in the colon. Products of carbohydrate  
6 fermentation in the colon include short chain fatty  
7 acids (SCFAs) and gasses like carbon dioxide,  
8 hydrogen and methane.

9  
10 Resistant starch takes a number of forms and simply  
11 resists hydrolysis by enzymes synthesised in the  
12 small intestine of man. This includes: small food  
13 particles entrapping starch; native starch;  
14 recrystallised (retrograded) starch and; chemically  
15 modified starch.

16  
17 If starches are hydrolysed (typically chemically  
18 with acids or enzymatically with  $\alpha$ -amylase and  
19 amyloglucosidase) smaller molecules called  
20 'dextrins' are generated. Products may be as small  
21 as the smallest possible monosaccharide glucose or  
22 be slightly hydrolysed but still polymeric. Glucose  
23 syrups are made from starch hydrolysis and contain  
24 variable proportions of sugars and dextrins  
25 depending on the nature and extent of conversion.  
26 The extent of conversion is usually defined as  
27 dextrose equivalence (DE) which equates reducing  
28 power of the hydrolysate to that of pure dextrose  
29 (glucose).

30  
31 Maltodextrins are DP20 or less, GRAS quality,  
32 tasteless and very soluble. They are easily

1 digestible and are used in energy drinks because of  
2 their solubility and reportedly relatively slow  
3 digestibility compared to glucose (which is simply  
4 absorbed). The difference in rate of glucose  
5 appearance in the blood as a consequence of drinking  
6 glucose or maltodextrin solutions is relatively  
7 small (e.g. ~45minutes) because of the extent of  
8 conversion of the maltodextrin.

9  
10 In the present invention, any suitable semi-  
11 crystalline or crystalline starch may be used. In  
12 preferred embodiments, the starch of and for use in  
13 the invention is a waxy starch.

14  
15 The starch may be a naturally produced starch or may  
16 be synthetically produced using any suitable method  
17 e.g. plant breeding or biotechnological methods  
18 (including transgenic technology etc.).

19  
20 Preferred native starches are waxy with an average  
21 diameter of approximately 15-35µm.

22

23

24 **Hydrothermally Treated Starch**

25

26 As discussed above and shown in the examples below,  
27 the inventors have found that particularly good  
28 results are obtained when using hydrothermally  
29 treated starch.

30

31 Two main methods are currently used for the  
32 hydrothermal treatment of starch: heat-moisture

1 treatment (high temperature, low moisture) and  
2 annealing (high moisture, low temperature).

3

4 **Heat Moisture Treated Starch (HMT Starch)**

5

6 Heat and moisture treated starch is typically  
7 produced by exposing moist starch (e.g. 15-30%  
8 moisture) to temperatures of e.g. 95°C to 130° for  
9 periods up to 30 hours (typically 16-24). These  
10 ranges do not exclude other heat-moisture profiles.  
11 For example, HMT starch for use in the invention may  
12 be produced by thermally treating starch in a sealed  
13 container under the following conditions: 20%  
14 moisture and 105°C for 16 hours. The treated starch  
15 may then be cooled to room temperature, air-dried  
16 and then passed through 300um sieve.

17

18 Such heat moisture treatment results in a number of  
19 significant property changes to starches. The extent  
20 of the effect varies with the type of starch but in  
21 general the effects are:

22

- 23 • increased gelatinisation temperature
- 24 • reduced water absorption and swelling power
- 25 • changed X-ray diffraction pattern
- 26 • increased enzyme susceptibility

27

28 As described herein, although heat moisture  
29 treatment results in starches having increased  
30 susceptibility to enzymatic degradation, the  
31 inventors have surprisingly shown that when used in  
32 methods of the invention, heat moisture treated

1       starches provide significantly greater prolongation  
2       of the time period over which serum glucose levels  
3       are maintained compared to the corresponding non  
4       heat moisture treated starches.

5

6       **Annealing Treatment of Starch**

7

8       In certain embodiments of the invention the starch  
9       of and for use in the invention is annealing treated  
10      starch. Any suitable annealing treated starch may  
11      be used.

12

13      Annealing is a process in which starch granules are  
14      treated for a relatively long time in excess amounts  
15      of water at a temperature slightly higher than room  
16      temperature. Typically, annealing of starch  
17      involves incubation of starch granules in water  
18      (>40% w/w), for a time period in the range 1 hour to  
19      10 days at a temperature between the glass  
20      transition and the gelatinisation temperature.  
21      Preferred annealing conditions are less than 10°C  
22      below the onset of gelatinisation temperature, in  
23      excess water for up to 7 days.

24

25      **Treatment/Therapy**

26

27      "Treatment" (which, unless the context demands  
28      otherwise, is used interchangeably with "therapy",  
29      includes any regime that can benefit a human or non-  
30      human animal. The treatment may be in respect of an  
31      existing condition or may be prophylactic

1        (preventative treatment). Treatment may include  
2        curative, alleviation or prophylactic effects.

3

4        **Food Compositions**

5

6        The invention extends to a therapeutic food  
7        composition for the treatment of diseases  
8        characterised by hypoglycaemic episodes, wherein  
9        said composition comprises a semi-crystalline  
10      starch.

11

12      The therapeutic food compositions of and for use in  
13      the present invention may consist solely of said  
14      starches or preferably may comprise further  
15      additives. Such additives may contribute merely to  
16      the palatability of the composition, e.g.  
17      flavourings, or may contribute significant calorific  
18      value, for example, sugars with a more rapid release  
19      profile than the starches, or lipids. These  
20      compounds may be incorporated to slow gastric  
21      emptying and facilitate the effect (e.g. amino  
22      acids, lipids etc.).

23

24      The therapeutic food composition can take a variety  
25      of forms, for example as a food, a food supplement,  
26      a liquid, an emulsion or mixture thereof.

27      Preferably, it is prepared as a ready to eat  
28      foodstuff, for example as a snackbar, a baked  
29      product, pasta or drink.

30

31      Alternatively, the therapeutic food composition may  
32      be administered as a pharmaceutical composition,

1 which will generally comprise a suitable  
2 pharmaceutical excipient, diluent or carrier  
3 selected dependent on the intended route of  
4 administration.

5

6 Some suitable routes of administration include (but  
7 are not limited to) oral, rectal or parenteral  
8 (including subcutaneous, intramuscular, intravenous,  
9 intradermal) administration.

10

11 For intravenous injection the active ingredient will  
12 be in the form of a parenterally acceptable aqueous  
13 solution which is pyrogen-free and has suitable pH,  
14 isotonicity and stability. Those of relevant skill  
15 in the art are well able to prepare suitable  
16 solutions using, for example, isotonic vehicles such  
17 as Sodium Chloride Injection, Ringer's Injection,  
18 Lactated Ringer's Injection. Preservatives,  
19 stabilisers, buffers, antioxidants and/or other  
20 additives may be included, as required.

21

22 However, the composition is preferably for  
23 administration orally. Pharmaceutical compositions  
24 for oral administration may be in tablet, capsule,  
25 powder or liquid form. A tablet may comprise a  
26 solid carrier such as gelatin or an adjuvant.  
27 Liquid pharmaceutical compositions generally  
28 comprise a liquid carrier such as water, petroleum,  
29 animal or vegetable oils, mineral oil or synthetic  
30 oil. Physiological saline solution, dextrose or  
31 other saccharide solution or glycols such as

1       ethylene glycol, propylene glycol or polyethylene  
2       glycol may be included.

3

4       Examples of the techniques and protocols mentioned  
5       above and other techniques and protocols which may  
6       be used in accordance with the invention can be  
7       found in Remington's Pharmaceutical Sciences, 16th  
8       edition, Oslo, A. (ed), 1980.

9

10      **Dose**

11

12      The therapeutic food compositions of and for use in  
13      the invention are preferably administered to an  
14      individual in a "therapeutically effective amount",  
15      this being sufficient to show benefit to the  
16      individual. The actual amount administered, and  
17      rate and time-course of administration, will depend  
18      on the nature and severity of what is being treated.  
19      Prescription of treatment, e.g. decisions on dosage  
20      etc, is ultimately within the responsibility and at  
21      the discretion of general practitioners and other  
22      medical doctors, and typically takes account of the  
23      disorder to be treated, the condition of the  
24      individual patient, the site of delivery, the method  
25      of administration and other factors known to  
26      practitioners.

27

28      The optimal dose can be determined by physicians  
29      based on a number of parameters including, for  
30      example, age, sex, weight, severity of the condition  
31      being treated, the active ingredient being  
32      administered and the route of administration.

1

2

3       The invention will now be described further in the  
4       following non-limiting examples. Reference is made  
5       to the accompanying drawings in which:

6

7       Figure 1 shows schematically glucose and glycogen  
8       metabolism reactions.

9

10      Figure 2 shows a comparison of the hydrolysis  
11      profile of native starches using the Karkalas et al  
12      (1992) procedure;

13

14      Figure 3 shows blood glucose level after consumption  
15      of native starches;

16

17      Figure 4 shows a comparison of the blood lactate  
18      level after consumption of native starches;

19

20      Figure 5 shows a comparison of blood glucose after  
21      consumption of two native starches (wheat and waxy  
22      maize) with added pregelatinised (maize) starch;

23

24      Figure 6 shows a comparison of the blood lactate  
25      level after consumption of two native starches  
26      (wheat and waxy maize) with added pregelatinised  
27      (maize) starch;

28

29      Figure 7 shows a comparison of blood glucose after  
30      consumption of starch (native waxy maize and  
31      soluble) encapsulated with pectin and alginate.

32

1      Figure 8 shows a comparison of blood lactate after  
2      consumption of starch (native waxy maize and  
3      soluble) encapsulated with pectin or alginate.

4  
5      Figure 9 shows a comparison of blood glucose after  
6      consumption of starch (native waxy maize, soluble)  
7      encapsulated with lipid.

8  
9      Figure 10 shows a comparison of blood glucose after  
10     consumption of heat-moisture treated waxy maize  
11     starch, waxy maize and normal maize starch.

12  
13     Figure 11 shows a comparison of blood lactate after  
14     consumption of heat-moisture treated waxy maize  
15     starch, waxy maize and normal maize starch.

16  
17     Figure 12 shows a comparison of digestibility of  
18     native and heat-moisture treated waxy maize  
19     starches.

20  
21     Figure 13 shows a comparison of digestibility of  
22     native and heat-moisture treated normal maize  
23     starches.

24  
25     **Example 1: In vitro hydrolysis**

26  
27     Common native starches (barley, maize, potato, rice  
28     and wheat) were evaluated using the Karkalas *et al*  
29     (1992) (*in vitro*) method to identify their amylase  
30     hydrolysis profile and potential for slow release of  
31     energy in individuals. These data are presented in  
32     Figure 2.

1  
2 As can be seen from Figure 2 that rice starch has a  
3 fast energy release profile initially followed by a  
4 much slower process. In contrast, potato and high  
5 amylose starches show great resistance towards  
6 amylase hydrolysis and are nearly untouched by the  
7 enzyme. Starches from normal maize, waxy maize and  
8 wheat show continuous slow release energy profile.  
9 These data provide the basis for an *in vitro*  
10 selection of the most appropriate starch for this  
11 purpose (as discussed later). Note that they do not  
12 define the rate or extent of hydrolysis in the  
13 actual gut but provide a means of ordering the rate  
14 of extent of hydrolysis based on the *in vitro*  
15 system.

16

17 **Example 2: Digestion of native starches**

18

19 Under clinical supervision, individuals suffering  
20 from GSD were fed 60g samples of native starches  
21 dispersed in semi-skimmed milk. The amount of blood  
22 glucose and lactate were monitored and are presented  
23 in Figures 3 and 4. Native potato starch was not  
24 consumed in view of its resistance to digestion (and  
25 cause of potential colonic disturbance accordingly).

26

27 These data show that waxy rice starch released  
28 glucose very quickly where the highest (too high)  
29 initial glucose peak ( $8.7 \text{ mmoll}^{-1}$ ) at 1 hour post  
30 ingestion was obtained. The blood glucose level then  
31 dropped to  $3\text{mmoll}^{-1}$  within 4.5 hours (270 minutes).  
32 Normal rice showed a much lower initial glucose peak

1 with a longer release profile corresponding to  
2  $3.2\text{mmoll}^{-1}$  within 5 hours (300 minutes) but less  
3 glucose released in the time course of the  
4 experiment compared to the waxy rice starch. High  
5 amylose starch too extensively restricted glucose  
6 release (although this could be moderated by  
7 physical/ chemical/ enzymatic or biotechnological  
8 modification). The normal maize starch ('corn  
9 starch') exhibited a low glucose peak 1 hour  
10 ( $6.6\text{mmoll}^{-1}$ ) after ingestion with an extended release  
11 of  $2.9\text{mmoll}^{-1}$  after 300 minutes. The waxy maize  
12 starch surprisingly showed the optimal release  
13 profile with less than  $7\text{mmoll}^{-1}$  blood glucose 1 hour  
14 post ingestion, a significant glucose release  
15 profile for up to 6 hours (330 minutes) which  
16 dropped to  $2.9\text{mmoll}^{-1}$  at this point.

17  
18 Lactate in the blood also reflected the starch  
19 consumed (Figure 4). The high amylose maize starch  
20 provided the least lactate response (highest  
21 lactate) as it was little digested (Figure 3). The  
22 greatest reduction in lactate was achieved by the  
23 waxy maize starch and in common with the previous  
24 data promotes its potential use for GSD and similar  
25 conditions requiring slow release of energy.

26  
27 Based on these data, there is clearly a granule size  
28 and compositional effect that regulates native  
29 starch hydrolysis to glucose in the gut. There is a  
30 balance between choosing a starch for therapy based  
31 on the 1 hour glucose peak, duration of release and

1 the amount (integrated area) of glucose release with  
2 time. A preferred starch for the purpose, therefore:

3

4 a) is highly crystalline (semi-crystalline) with  
5 waxy starches providing the most appropriate  
6 crystalline (amylopectin) matrices for this purpose.

7

8 b) has reasonably large granules without exceeding  
9 the digestive capacity. Rice starches (~5 $\mu\text{m}$  diameter  
10 on average) are too small. Maize starch granules are  
11 preferred (~20-25 $\mu\text{m}$  diameter on average).

12

13 It is recognised that the cereal starches contain  
14 lipid and that other starches may be more  
15 appropriate in terms of size and composition.  
16 However, in view of the lack of digestibility and  
17 potential dangers of eating large granules (which  
18 may cause colonic lesions) it is proposed that  
19 granules in excess of ~40 $\mu\text{m}$  diameter are not  
20 consumed for this purpose.

21

22 **Example 3: Digestion of native starches in the  
23 presence of a pre-gelatinised starch thickener**

24

25 Under clinical supervision, individuals suffering  
26 from GSD were fed 60g samples of two native starches  
27 (wheat or waxy maize), each sample containing 54g of  
28 either starch and 6g pregelatinised maize starch  
29 (National B37, National Starch & Chemical) dispersed  
30 in cold semi-skimmed milk. The amount of blood  
31 glucose and lactate were monitored and are presented  
32 in Figures 5 and 6.

1  
2 These data show that even in the presence of  
3 amorphous (pre-gelatinised) starch the waxy maize  
4 starch resists digestion (Figure 5) more than the  
5 wheat starch, which contains a bi-modal distribution  
6 of small (~10 $\mu$ m average diameter) and large (~25 $\mu$ m  
7 average diameter) granules but with similar  
8 composition (amylose, lipid, moisture and protein).  
9 This is reflected in a lower blood lactate (even  
10 though the patients started with a higher lactate  
11 content when presented with the waxy maize starch  
12 (as shown in Figure 6)). The importance of this work  
13 is that it shows that even if the waxy starch is  
14 mixed with other materials that have the capacity to  
15 provide a quicker glucose response it can still  
16 provide a slow release function.

17

18 **Example 4: Digestion of native starches in the**  
19 **presence of non-starch polysaccharides**

20

21 Native waxy maize starch (Amioca Powder T, National  
22 Starch) was encapsulated in soluble starch (Crystal  
23 Tex 626, National Starch) and pectin (LM-104AS-FS,  
24 CPKelco) or alginic acid (Manugel GMB, Manugel)  
25 according to Tester and Karkalas (1999). The final  
26 starch to non-starch polysaccharide (NSP) ratio was  
27 5.7:1 or 19:1. The proportion of the soluble starch  
28 to native starch varied according to the proportion  
29 of native starch used for the two conditions but was  
30 the same for both non-starch polysaccharide  
31 conditions and simply serves as a comparison.

32

1 Under clinical supervision, individuals suffering  
2 from GSD were fed 70g or 63g (depends on the starch  
3 to NSP ratio) samples of NSP encapsulated starch  
4 dispersed in cold semi-skimmed milk. The amount of  
5 blood glucose and lactate were monitored and are  
6 presented in Figures 7 and 8.

7  
8 These data show that, although the amount of starch  
9 modifies the extent of glucose release as expected,  
10 the alginate or pectin components do not stretch out  
11 the release profile much beyond 5 hours (300  
12 minutes). Hence, the presence of a non-starch  
13 polysaccharide 'raft' or food matrix is not enough  
14 in itself to slow the rate of starch hydrolysis  
15 accordingly (whether native or soluble). The blood  
16 lactate response reflects the blood glucose where  
17 alginate appears to reduce lactate production more  
18 markedly than pectin (since it restricts hydrolysis  
19 more).

20  
21 **Example 5: Digestion of native starches in the**  
**presence of lipid**

22  
23 Starch (Amioca Powder T, National Starch) with or  
24 without addition of soluble starch (Crystal Tex 626,  
25 National Starch) was encapsulated in lipid (Revel A,  
26 Loders Croklaan B. V.) as follows. The lipid was  
27 dissolved in the minimal amount of ethanol possible  
28 to dissolve the starch. The starch was then  
29 thoroughly mixed with the ethanol solution until  
30 homogeneous. The starch was laid on a tray and air  
31 at 35°C was allowed to flow over the

1       ethanol/lipid/starch system (in a fume cupboard)  
2       until the ethanol had all evaporated from the  
3       system. The final starch to lipid ratio was 9:1.  
4       When used, the proportion of soluble starch was 10%  
5       of the total starch fraction.

6

7       Under clinical supervision, individuals suffering  
8       from GSD were fed 66g samples of lipid encapsulated  
9       starch dispersed in cold semi-skimmed milk. The  
10      amount of blood glucose was monitored and is  
11      presented in Figures 9.

12

13      These data show that the lipid restricts the amount  
14      of starch digestion at all times (see previous  
15      figures for comparison). Overall, this approach is  
16      not appropriate for the control of glucose release  
17      (extent of hydrolysis) from the starch as the amount  
18      released over time and the actual duration is  
19      reduced.

20

21      **Example 6: Digestion of hydrothermally treated  
22      starches.**

23

24      Starch (Amioca Powder T, National Starch) was  
25      thermally treated in a sealed container under the  
26      following conditions: 20% moisture and 105°C for 16  
27      hours. The treated starches were then cooled to room  
28      temperature, air-dried and then passed through 300µm  
29      sieve.

30

31      Under clinical supervision, individuals suffering  
32      from GSD were fed 60g or 90g samples of heat-

1 moisture treated starch dispersed in cold semi-  
2 skimmed milk. The amount of blood glucose and  
3 lactate were monitored and are presented in Figures  
4 10 and 11.

5

6 These data show that:

7

8 (i) Heat moisture treated (HMT) waxy maize starch  
9 has a much reduced initial glucose response at  
10 60 minutes than native waxy maize starch  
11 (Figure 10).

12 (ii) Because of the reduced initial response more  
13 can be fed to be within acceptable levels of  
14 glucose increase at this time (where a  
15 preferred response is  $<8\text{mmol l}^{-1}$ ).

16 (iii) As a consequence of the above, greater  
17 amounts could be fed (90g versus 60g) leading  
18 to 7.5 hour (450 minutes) profile where the HMT  
19 starch can still maintain the blood glucose at  
20  $\sim 2.5\text{mmol l}^{-1}$ .

21 (iv) The glucose response provides an acceptable  
22 and desirable lactate response accordingly  
23 (Figure 11).

24

25 Similar results were obtained when repeating the  
26 experiments on further patients (results not shown).

27

28 These data are reinforced by the in vitro assay as  
29 shown in Figure 12. Here the HMT treatment can be  
30 shown to clearly restrict the hydrolysis of the waxy  
31 maize starch.

32

1       Hence, the combination of a waxy starch and its heat  
2       moisture treatment allows for the formation of a  
3       desirable slow release of glucose therapy. The waxy  
4       maize starch is potentially more crystalline than  
5       normal or high amylose starches in view of the high  
6       amylopectin content.

7

8       A particularly preferred type of starch for this  
9       purpose is: semi crystalline with, preferably, the  
10      highest proportion of crystallinity possible and  
11      with amylase accessibility enhanced by the heat  
12      moisture processing.

13

14      Moreover, in order to show that the advantages  
15      conferred by hydrothermal treatment is not limited  
16      to waxy starches, the digestibility of native and  
17      heat-moisture treated normal maize starch was tested  
18      using the same assay as in Figure 12. The results  
19      are shown in Figure 13. As shown in Figure 13,  
20      hydrothermal treatment of normal maize starch (i.e.  
21      non-waxy starch) improves the hydrolysis profile of  
22      the starch. Thus, the results support the use of  
23      hydrothermally treated normal starch for slow  
24      release glucose therapy in the methods of the  
25      invention.

26

27      All documents referred to in this specification are  
28      herein incorporated by reference. Various  
29      modifications and variations to the described  
30      embodiments of the inventions will be apparent to  
31      those skilled in the art without departing from the  
32      scope and spirit of the invention. Although the

1 invention has been described in connection with  
2 specific preferred embodiments, it should be  
3 understood that the invention as claimed should not  
4 be unduly limited to such specific embodiments.  
5 Indeed, various modifications of the described modes  
6 of carrying out the invention which are obvious to  
7 those skilled in the art are intended to be covered  
8 by the present invention.

9

10

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